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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,702	01/17/2006	Junichi Kawakami	236211	9790

23460 7590 11/07/2007

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	**PAPER NUMBER**
4173	
MAIL DATE	**DELIVERY MODE**
11/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,702	KAWAKAMI, JUNICHI	
	Examiner	Art Unit	
	Marcos L. Sznaidman	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *7-10,20,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III (claims 11-12 and 21-26) drawn to a method for preventing and/or treating multiple sclerosis, meningitis, cerebritis, or brain abscess, which method comprises administering a compound of Formula I, in the reply filed on September 21, 2007 is acknowledged. The traversal is on the ground(s) that there is not undue burden to examine all claims in Groups II and III. This is not found persuasive because searching for a method of inhibiting blood-brain barrier disruption using compound I (Group II), does not necessarily overlap searching for a method of treating multiple sclerosis, meningitis, cerebritis, or brain abscess, using compound I. In other words, searching for inhibitors of blood-brain barrier disruption will not bring most of the answers related to treating multiple sclerosis, meningitis, cerebritis, or brain abscess an *vice versa*, so separate searches will be required. The search for the structures related to compound I will definitively not result in all the answers related to inhibiting blood-brain barrier disruption or a method of treating multiple sclerosis, meningitis, cerebritis, or brain abscess. For example searching for 3-methyl-1-phenyl-2-pyrazolin-5-one (compound I) and blood-brain barrier retrieved among others the following reference also cited by applicant: Watanabe et. al. (The Journal of Pharmacology and Experimental Therapeutics, 1994, 268:1597-1604) which describes the effect of compound I on the blood-brain barrier but does not mention any treatment of multiple sclerosis, meningitis, cerebritis, or brain abscess.

Applicant election of the following species: 3-methyl-1-phenyl-2-pyrazolin-5-one, as the compound of Formula I, is also acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 1-6 and 13-19 have been canceled.

Claims 7-12 and 20-28 are currently pending and are the subject of this office action.

Claims 7-10, 20, and 27-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 21, 2007.

Claims 11-12 and 21-26 are presently under examination.

Priority

The present application is a 371 of PCT/JP04/00105 filed 01/09/2004, and claims priority to foreign application: Japan 2003-004813 filed 01/10/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 and 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description Rejection.

Claims 11-12 and 21-26 recite a method for treating (claims 11-12 and 21-22) or preventing (claims 23-26) multiple sclerosis, meningitis, cerebritis, or brain abscess which comprises administering to a mammal at risk of developing multiple sclerosis, meningitis, cerebritis, or brain abscess, an effective amount of a pyrazolone derivative (3-methyl-1-phenyl-2-pyrazolin-5-one) represented by the formula (I) or a physiologically acceptable salt thereof, or a hydrate thereof or a solvate thereof.

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention....one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

While the specification describes the compound of formula I: 3-methyl-1-phenyl-2-pyrazolin-5-one, it does not describe any solvate as to convey possession of the entire genus encompassed by a solvate thereof.

Given the broad scope of the claimed subject matter, Applicant has not provided sufficient written description that would allow the skilled artisan to recognize all the solvates of 3-methyl-1-phenyl-2-pyrazolin-5-one claimed.

Claims 23-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement Rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

Claims 23-26 recite: a method for preventing multiple sclerosis, meningitis, cerebritis, or brain abscess which comprises administering to a mammal at risk of developing multiple sclerosis, meningitis, cerebritis, or brain abscess, an effective amount of a pyrazolone derivative (3-methyl-1-phenyl-2-pyrazolin-5-one) represented by the formula (I) or a physiologically acceptable salt thereof, or a hydrate thereof or a solvate thereof. However, the specification fails to disclose any data to support the fact that using this methodology could prevent any of the above-mentioned diseases. There is also no precedent in the literature that this type of treatment could prevent any of these diseases.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and prevention of multiple sclerosis, meningitis, cerebritis, or brain abscess are considered to be unpredictable factors. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable). Although prior art offers evidence for the treatment of multiple sclerosis, meningitis, cerebritis, or brain abscess, there is no evidence that any of these diseases could be prevented by any treatment. As illustrative of the state of the art, the examiner cites Butler (MEDLINE accession number 2006742380, PubMed ID: 17177931, corresponds to International Honor Society of Nursing, 2006, 3:185-93) and Sadvonick (MEDLINE accession number 93244497, PubMed ID: 8481562, corresponds to Current Opinion in Neurology and Neurosurgery, 1993, 6: 189-194).

Butler teaches that: "the published literature is severely limited in the area of meningococcal meningitis prevention programs in the at-risk college student population" (see subsection: conclusions and implications in the abstract section).

Sadovnick teaches that the cause of multiple sclerosis is unknown (see abstract). Prevention of a disease for which the causes are not known will be very difficult.

2. The amount of direction or guidance provided and the presence or absence of working examples

The specification fails to disclose any data to support the fact that using this method could prevent any disease like multiple sclerosis, meningitis, cerebritis, or brain abscess. Applicant provides experimental details that demonstrate that 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone) protects the blood-brain barrier system from getting disrupted, thereby resulting in improvement of neurological symptoms observed in multiple sclerosis models; but this result does not indicate that this compound could prevent the onset of multiple sclerosis, meningitis, cerebritis, or brain abscess.

3. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the ordinary skilled artisan would not accept the assertion that the instantly claimed compound (edaravone) could be predictably used for the prevention of multiple sclerosis, meningitis, cerebritis, or brain abscess. To determine if the claimed compound would prevent multiple sclerosis, meningitis, cerebritis, or brain abscess, would require formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in

an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by applicants.

Accordingly, the inventions of claims 23-26 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11-12 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Bourrie et. al. (PNAS, 1999, 96:12855-12859) in view of Watanabe et. al. (The Journal of Pharmacology and Experimental Therapeutics, 1994, 268:1597-1604, cited by applicant).

Claims 11-12 and 21-22 recite: "a method for treating multiple sclerosis, meningitis, cerebritis, or brain abscess which comprises administering to a mammal having multiple sclerosis, meningitis, cerebritis, or brain abscess, an effective amount of a pyrazolone derivative (3-methyl-1-phenyl-2-pyrazolin-5-one) represented by the formula (I) or a physiologically acceptable salt thereof, or a hydrate thereof or a solvate thereof".

For instant claims 11-12 and 21-22 Bourrie et. al teach that: "Experimental autoimmune encephalomyelitis (EAE) is a T cell autoimmune disorder that is a widely used animal model for multiple sclerosis (MS) and, as in MS, clinical signs of EAE are associated with blood-brain barrier (BBB) disruption. SR-57746A, a nonpeptide drug without classical immunosuppressive properties efficiently protected the BBB and impaired intrathecal IgG synthesis (two conventional markers of MS exacerbation) and consequently suppressed EAE clinical signs. This compound inhibited EAE-induced spinal cord mononuclear cell invasion and normalized tumor necrosis factor a and IFN-g mRNA expression within the spinal cord. These data suggested that pharmacological intervention aimed at inhibiting proinflammatory cytokine expression within the central nervous system provided protection against BBB disruption, the first clinical sign of EAE and probably the key point of acute MS attacks. This finding could lead to the

development of a new class of compounds for oral therapy of MS, as a supplement to immunosuppressive agents." (see abstract). In other words, Bourrie et. al. clearly teaches that compounds that provide protection against blood-brain barrier dysfunction are good candidates for the treatment of multiple sclerosis. Bourrie et. al. do not teach the treatment of multiple sclerosis by administering 3-methyl-1-phenyl-2-pyrazolin-5-one. However, Watanabe et. al. teach that: "3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186) mitigated dysfunction of the blood-brain barrier" (see abstract lines 6-7).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Bourrie et. al, (that indicates that compounds that provide protection against blood-brain barrier dysfunction are good candidates for the treatment of multiple sclerosis), with the teachings of Watanabe et. al, (that indicates that 3-methyl-1-phenyl-2-pyrazolin-5-one reduces dysfunction of the blood-brain barrier), with the motivation of developing a treatment for multiple sclerosis by administering to a patient 3-methyl-1-phenyl-2-pyrazolin-5-one; thus resulting in the practice of claims 11-12 and 21-22 with a reasonable expectation of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcos L. Sznaidman whose telephone number is 571 270-3498. The examiner can normally be reached on Monday through Friday 9 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MLS
October 31, 2007

11/6/07
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SUPERVISORY PATENT EXAMINER